THE SYNTHESIS OF RUGOSINONE AND LEDECORINE

Natesan Murugesan and Maurice Shamma*

Department of Chemistry, The Pennsylvania State University,

University Park, Pennsylvania 16802

Hydrolysis with concomitant air oxidation of polyberbine (5), derived from berberine chloride (6), furnished dihydrorugosinone (7) which underwent further air oxidation in ethanolic sodium hydroxide to give rugosinone (2). m-Chloroperbenzoic acid oxidation of coptisine chloride (8) afforded enamide 9 whose successive reduction using lithium aluminum hydride in THF and sodium borohydride in methanol supplied a mixture of norledecorine (10) and ledecorine (3). N-Methylation of 10 with formaldehyde and sodium borohydride gave rise to ledecorine (3) in high yield. Polycarpine (1), rugosinone (2), and ledecorine (3) probably arise in nature from protoberberines.

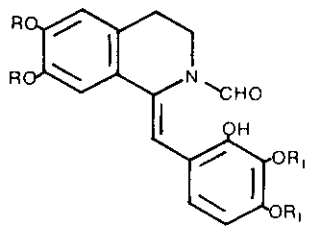
Benzylisoquinolines presently known which incorporate three oxygenated substituents in the bottom ring are polycarpine (1) found in Enantia polycarpa Engl. et Diels (Annonaceae),[1] rugosinone (2) recently obtained from Thalictrum rugosum Ait. (Ranunculaceae),[2] and (-)-ledecorine (3) present in Corydalis ledebouriana K. et K. (Fumariaceae).[3] Another common feature of alkaloids 1-3 is that they possess a phenolic group at C-2' in the bottom ring. They differ, however, not only in the nature of the aromatic substituents, but more significantly in the state of the nitrogen and in the degree of oxidation of the α-carbon atom.

The biogenetically patterned synthesis of polycarpine (1) from palmatine chloride (4) has already been described, as well as that of the analog 5 - here named polyberbine - starting with berberine chloride (6).[4] In each of these transformations, m-chloroperbenzoic acid was used to oxidize the appropriate protoberberinium salt.

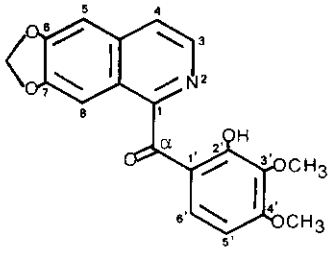
In order to carry out a biogenetic type synthesis of rugosinone (2), polyberbine (5) was dissolved in methanol, and the solution allowed to stand for one to two weeks. The initial enamine obtained from this hydrolysis suffered facile air oxidation under the mild conditions used so that the product, obtained in 20% yield, proved to be 3,4-dihydrorugosinone (7), $C_{19}H_{17}O_6N$, which crystallized from methanol as light yellow crystals, mp 172-174° C, $\nu_{max}^{CHCl_3}$ 1620 cm^{-1}. Air oxidation of dihydrorugosinone in hot ethanolic sodium hydroxide[5] provided a 90% yield of the desired rugosinone (2) as light yellow needles, mp 220-221° C (ethyl acetate), literature mp 223-224° C (ethyl acetate), identical with the natural product.[2]

The synthesis of ledecorine (3) from coptisine chloride (8)[6] was achieved through m-chloroperbenzoic acid in methylene chloride oxidation of 8 followed by work-up to afford the colorless and amorphous enamide 9 in 40-50% yield, $C_{19}H_{15}O_6N$, $\nu_{max}^{CHCl_3}$ 1660 cm^{-1}. Lithium aluminum hydride reduction of 9 in THF, immediately followed by further reduction with sodium borohydride in methanol, furnished a 35% yield of oily, racemic, norledecorine (10), $C_{18}H_{17}O_5N$, together with a 28% yield of the desired racemic ledecorine (3), $C_{19}H_{19}O_5N$, as a colorless gum whose spectral data are in general agreement with the natural product.[3] Furthermore, N-methylation of racemic norledecorine (10) using formaldehyde and sodium borohydride led to ledecorine in 80% yield.

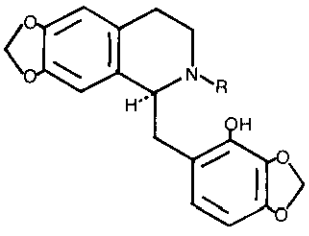
Polycarpine (1), rugosinone (2), and (-)-ledecorine (3), must arise in nature from oxidation of protoberberinium salts. The biogenesis of the highly oxidized rugosinone (2) most probably parallels the route used here for its synthesis. It is not presently clear, however, if (-)-ledecorine (3) is formed in nature through the intermediacy of enamide 9 or from a direct Umezawa-type oxidation of tetrahydrocoptisine at C-8a which would result in cleavage of the critical C-8 to C-8a bond to furnish directly a tetrahydrobenzylisoquinoline.[7,4]



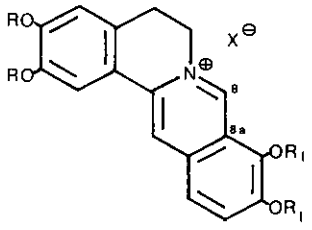
1, R = R_1 = CH_3
5, R + R = CH_2, R_1 = CH_3
9, R + R = R_1 + R_1 = CH_2



2
7, 3,4-dihydro-2



3, R = CH_3
10, R = H



4, R = R_1 = CH_3
6, R + R = CH_2, R_1 = CH_3
8, R + R = R_1 + R_1 = CH_2

Spectral Data for the Benzylisoquinolines

3,4-Dihydrorugosinone (7): λ_{max}^{EtOH} 230sh and 298 nm (log ε 4.36 and 4.23); nmr ($CDCl_3$) δ2.41 (2H, t, J = 6 Hz, $ArCH_2$), 3.82 (2H, t, J = 6 Hz, CH_2N), 3.92 (6H, s, $2xOCH_3$), 5.90 (2H, s, OCH_2O), 6.40 (1H, d, J = 9.0 Hz, ArH), 6.60 (1H, s, ArH), 6.72 (1H, s, ArH), 7.40 (1H, d, J = 9.0 Hz, ArH); ms m/e 355 (M^+), 326, 296 (base), 181, 176, 174, 172, 164 and 151.

Enamide 9: λ_{max}^{EtOH} 220, 263sh and 330 nm (log ε 4.33, 3.83 and 3.93); nmr ($CDCl_3$) δ2.80 (2H, t, J = 6 Hz, $ArCH_2$), 3.87 (2H, t, J = 6 Hz, CH_2N), 5.83 (2H, s, OCH_2O), 5.88 (2H, s, OCH_2O), 6.35 (1H, d, J = 9 Hz, ArH), 6.50 (1H, s, ArH), 6.68 (1H, d, J = 9 Hz, ArH), 6.70 (1H, s, ArH), 7.17 (1H, s, ArH), and 8.01 (1H, s, NCHO); ms m/e 353 (M^+), 336, 335, 325 (base), 324, 308, 280, 278, 250 and 238.

(±)-Norledecorine (10): λ_{max}^{EtOH} 240sh and 292 nm (log ε 3.91 and 3.55); ms m/e 327 (M^+), 176 (base), 164, 151 and 148.

(±)-Ledecorine (3): λ_{max}^{EtOH} 240sh and 292 nm (log ε 3.89 and 3.53); nmr ($CDCl_3$, 200 MHz, FT) δ2.58 (3H, s, NCH_3), 4.10 (1H, m, H-1), 5.91 and 5.92 (2H, apparent d, OCH_2O), 5.93 (2H, s, OCH_2O), 6.22 (1H, d, 7.9 Hz, ArH), 6.41 (1H, d, 7.9 Hz, ArH), 6.50 (1H, s, ArH) and 6.60 (1H, s, ArH); ms m/e 341 (M^+), 190 (base), 176 and 149.

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References and Notes

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